



At Polio's End Game, Strategies Differ

Brian Vastag

BALTIMORE—As a young student, Walter Orenstein, MD, head of the US National Immunization Program, idolized Jonas Salk, MD. Orenstein's favorite story about the discoverer of one polio vaccine takes place at a meeting where the well-known friction between Salk (who died in 1995) and the other polio vaccine discoverer, Albert Sabin, MD (who died in 1993), came to a head. As participants debated the merits of the Salk and Sabin vaccines, Salk stood up and said, "There is something we can agree on. The world needs just one vaccine."

The world eventually got Sabin's, to the tune of hundreds of millions of

doses. Since the 1988 launch of a worldwide eradication campaign, the Sabin oral polio vaccine (OPV) has cut the number of new cases by 99%, saving some 3 million children from paralysis. But for Orenstein, who was here to deliver the University of Maryland's annual "Frontiers in Vaccinology" lecture, "the final 1% will be the hardest."

Now, at a time when extinction of the wild virus is all but certain, with just under 3000 new cases reported worldwide in 2000, public health veterans in charge of what they call the largest medical operation in history are preoccupied with what to do after eradication.

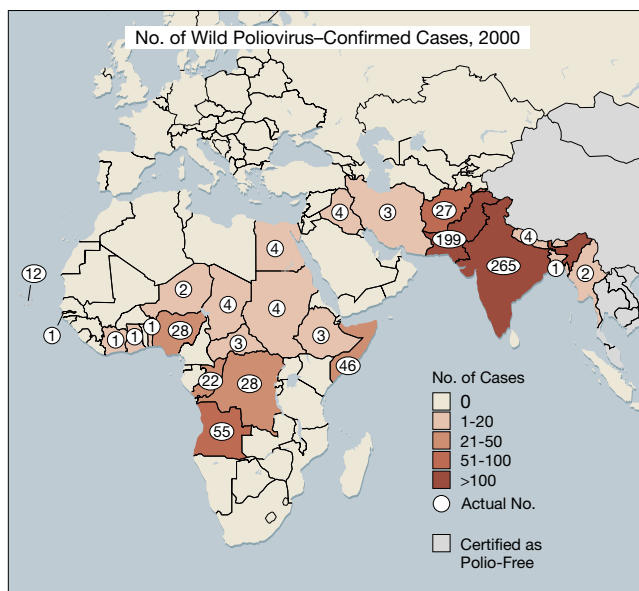
It's not that they don't want to celebrate. It's that after 2005, when the World Health Organization (WHO) is

expected to declare the virus eradicated, the path to polio's true end veers into forests thicker than first glance suggests.

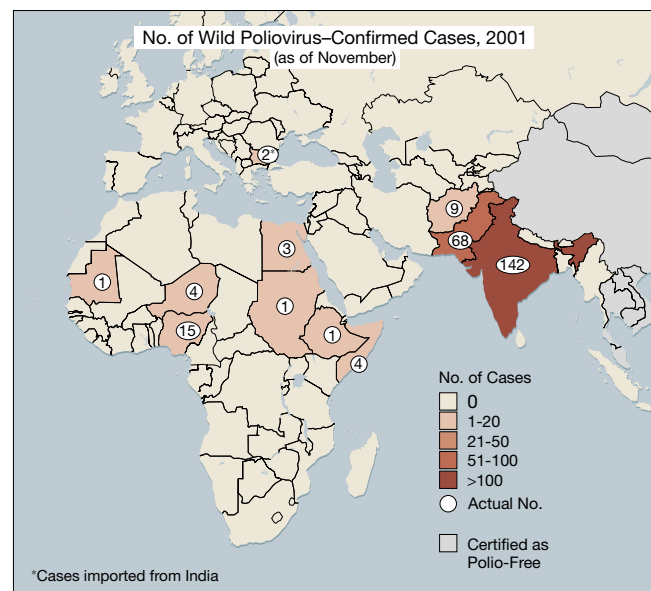
Originally the primary partners—WHO, the Centers for Disease Control and Prevention (CDC), UNICEF, and Rotary International—had planned an abrupt end to international immunization. But last year's outbreak of vaccine-induced polio on the island of Hispaniola—13 cases in the Dominican Republic and eight in Haiti—fractured that plan.

"BACKMUTATING"

Polio experts have known for decades that OPV, which uses a live attenuated virus, can cause polio. In fact, as



Source: World Health Organization



Troubled countries in Africa and Asia remain the last frontier for polio eradication efforts. The Americas and the Western Pacific, including China, are WHO-certified as polio-free, meaning no wild virus has been detected during 3 years of active surveillance. Europe could achieve certification by 2002.



UNICEF/DHQ089/Shehzad Noorani



As a group of women and children await their turn during the NIDs campaign, several older brothers present infants to receive polio vaccine near the Afghanistan-Pakistan border town of Torkham in Khyber Agency, a tribal area in Pakistan's North West Frontier Province.

far back as 1977 the Institute of Medicine noted that vaccine-caused polio outstripped natural cases in the United States.

But on Hispaniola, the virus did what had been predicted but never seen, namely “backmutating” to a communicable strain. (See p 2802.) Any doubts about the outbreaks’ origin disappeared after genetic sequencing found the Hispaniola virus to be 97% similar to the Sabin strain. As this new virus spread across the island, it shed from the unimmunized population, growing meaner and meaner with each hop. After 2 or 3 years, it had regained its virulence.

At a CDC vaccine advisory panel meeting last spring, a concerned Olen Kew, MD, of the National Center for Infectious Diseases, said, “We clearly need to do more research to see if this is a rare event.”

So far it appears to be. However, Orenstein did note two other vaccine-caused outbreaks. Egypt experienced 30 or so cases in the 1980s, discovered after the fact by Kew and others, and earlier this year the Philippines reported three cases. These unexpected infections alarmed health officials and led to a rift in polio “end game” planning.

“The goal was to simply stop using OPV,” said Orenstein. “But now that’s harder than any of us anticipated.”

TWO CAMPS—AND COMPLICATIONS

One camp, which includes D. A. Henderson, MD, MPH, the man who led the massive campaign to eradicate wild smallpox and who was recently named director of the new federal Office of Public Health Preparedness, favors continuing oral vaccination indefinitely. Henderson is worried about three transmission vectors: the vaccine itself, bioterrorism, and accidental release from laboratory stocks. “We know that a risk factor for the vaccine [strain] circulating and causing paralysis is a susceptible population,” said Bruce Aylward, MD, the WHO’s coordinator of the worldwide eradication effort. “In a highly immunized population, that won’t happen.”

Skeptics say that scenario recalls the serpent Ouroboros, a creature that eats its own tail. It means vaccinating children against—vaccination. Some health policymakers, notably those from developing countries, oppose the plan as unethical and unneeded. Many want to discard OPV as soon as possible. The risk—no matter how small, they say—is unacceptable in the absence of natural

disease. But complications arise in this scenario as well. As seen on Hispaniola, the virus strain can circulate for a few years before regaining virulence. If the world simply halted all oral vaccination, reservoirs of potentially dangerous virus could still be lurking.

As the top polio policymaker, Aylward remains unfazed. “As in all such situations, the truth or reality lies somewhere in between,” he said in a phone interview from Atlanta, hours before returning to Geneva to chair a critical meeting on the topic.

One option, said Roland Sutter, MD, chief of polio eradication at the CDC, is a “big bang” worldwide immunization push followed by country-to-country voluntary vaccination. Nations deciding to continue immunization would switch to the safer, killed-virus injectable polio vaccine (IPV). This plan also provides increased surveillance for outbreaks. Should one occur, quick response teams would quickly quash it with vaccine from new stockpiles, said Orenstein.

Another strategy calls for switching the entire world to IPV for a set period, allowing OPV strains to die off while maintaining population immunity. At first glance, this strategy looks ideal. But delivering injected vaccines to poor, remote fringes of civilization poses a number of problems. While the OPV campaign recruits hundreds of thousands of community volunteers to simply squeeze a few drops into a child’s mouth, building an army of health workers to inject 600 million or more children each year is almost inconceivable, said Orenstein.

On top of that, dose for dose, OPV delivers better immunity than IPV. The injected vaccine works best when delivered at 2, 4, and 6 months of age. After factoring in a less optimal schedule, a likely situation in much of the world, seroconversion rates would be “lousy,” perhaps lower than 50%, said Aylward. “You could end up paying a lot of money for a little insurance.” Finally, IPV is several times more expensive, though the price could drop with bulk public sector purchases.



VARYING SOLUTIONS

To overcome these problems, experts are devising variations on the theme. Some call for “pulsed” IPV vaccination. Instead of continuously tracking down every child for a jab, smaller cohorts of children would be immunized as a “wall” to stop mutated virus breakthrough. (Cuba and Hungary have successfully used this approach.) Ultimately, a killed-virus oral vaccine would be ideal, but Orenstein and others perceive little support for this long-term research-intensive solution.

While polio workers plot these strategies, deadlines approach. The World Health Assembly, responsible for the ultimate decisions, has asked for new data by the end of 2002. Among other items, the assembly wants information on the feasibility of manufacturing and purchasing huge batches of IPV. The multinational body also wants data on OPV transmission risk. By the end of 2003, it wants data on how and why OPV backmutates, on whether IPV immunizations will actually stop Sabin-strain outbreaks, and on the feasibility of delivering IPV to children in developing nations.

Defeating Disease Despite Devastation

In early November some 40,000 Afghan volunteers fanned out across their ravaged, rocky country focused on a simple goal: delivering oral polio vaccine to as many children as possible. They sought out families afflicted by war and refugees bunched near the Pakistani border. Two months earlier the volunteers had reached an astonishing 5 million Afghan children, nearly 88% of those under age 5, in less than a week.

The push, part of UNICEF's global campaign, is aimed at finishing off polio in Afghanistan, which reports just nine confirmed cases this year. The 50 full-time Afghan UNICEF staff who recruit and direct the community volunteers are reaching this remarkable target despite two decades of war, a horrendous 3-year drought, and an ever-shifting, seminomadic populace.

The September “national immunization days” (NIDs) had long been scheduled for the region, but arrived at a time of imminent war. “They said, ‘Hey, we’ve made a huge investment and we want to continue immunizing our children,’” said Bruce Aylward, MD, the World Health Organization’s director of the polio eradication programs. “It was an extraordinary activity.”

And in November, after a month of war, Aylward said that his team started to think the second round of immunization days would never move ahead. Once again, though, the workers in Afghanistan and Pakistan responded with action. “It was extraordinary,” said Aylward.

Central Asia remains one of the last reservoirs of wild polio virus. This year, Pakistan and Afghanistan account for 20% of cases worldwide. A UNICEF spokesperson said the agency is collecting reports on the November immunization days for release by the end of the year. The agency expects polio to vanish from the region soon thereafter.—B.V.

Aylward acknowledged that as this information flows in, political and economic jockeying will push science aside. As that tricky stage of the end game approaches,

perhaps he will take solace in Jonas Salk’s likely reaction: “There is one thing everyone can agree on. The world needs just one polio eradication policy.” □

Cardiologists Like Statins —More Than Patients Do

Mike Mitka

ANAHEIM, CALIF—In the largest study to date, researchers show that statin therapy to reduce the risk of major vascular events works well in patients at high risk for heart disease. But getting patients to comply with the treatment continues to be a problem, said other investigators.

At the annual Scientific Sessions of the American Heart Association, Rory Collins, MD, of the University of Oxford and lead author of the MRC/BHF Heart Protection Study, said this study showed that statin therapy reduces the risk of myocardial infarction (MI) and

ischemia by at least one third across a broad range of patients at high risk for heart disease. The results were seen even in patients with cholesterol readings below national target levels.

“These benefits are seen across this huge range of high-risk individuals—male, female, young, old—and irrespective of their cholesterol level,” said Collins. “I think this will change the way we practice medicine in terms of reducing risk in these high-risk individuals.”

YOU CAN PRESCRIBE IT . . .

The trial enrolled 20,536 patients, aged 40 to 80 years, from 69 hospitals in the

United Kingdom (UK). Participants were randomly allocated to receive simvastatin (40 mg daily) or placebo for 5.5 years. Enrolled were 5,082 women and 15,454 men. Of these, 4,893 were aged 65 to 69 years and 5,804 were aged 70 to 80 years. Total cholesterol was less than 194 mg/dL in 4,072 patients and low-density lipoprotein (LDL) cholesterol was less than 116 mg/dL in 6,793.

After allowing for noncompliance (including nonstudy statin use), the investigators found that simvastatin produced reductions in major vascular events in a broad range of patients. The findings showed that statin therapy reduced risk in patients for whom there



was uncertainty about the effectiveness of cholesterol-lowering therapy—women, people over age 70, those with LDL below 116 mg/dL, people with diabetes, and those with noncoronary occlusive disease.

“These results are as important as those results for aspirin,” Collins said, referring to studies in the 1980s showing that aspirin reduced the risk for MI. “Statins are the new aspirins, but it’s not an either/or because statins add to the benefits of aspirin and other treatments.”

Collins’ study found that after about 5 years, statin treatment prevented MI, ischemia, or other major vascular events in 100 of every 1000 people with previous MI, 80 of 1000 with angina or other evidence of coronary heart disease, 70 of 1000 with previous ischemia, 70 of 1000 with occlusive disease in a leg or other arteries, and 70 of 1000 with diabetes.

The study was funded by the United Kingdom’s Medical Research Council, the British Heart Foundation, Merck & Co Inc, and Roche Vitamins Ltd.

A clinically significant point, Collins suggested, is that physicians should not eliminate or fail to recommend cholesterol-lowering therapy in patients who have reached, or are below, national targets (in the United States, the National Cholesterol Education Program sets an LDL target level of ≤ 100 mg/dL).

“It’s important that measurement doesn’t actually prevent those patients from getting a treatment that we’ve now shown, for the first time, produces substantial benefits in these high-risk individuals—even those below the current national guidelines,” said Collins.

He said his findings suggest that in comparison with the current 25 million patients now taking therapy worldwide, about 200 million might benefit from treatment with statins.

Another study finding was that antioxidant vitamins produced no evidence of any benefit or harm. The researchers gave half of each treatment group a daily dose of 600 mg of vita-

min E, 250 mg of vitamin C, and 20 mg of β -carotene without observing any difference in the rates of deaths, MIs, ischemia, or other vascular disease outcomes.

BUT WILL THEY SWALLOW IT?

As welcomed as the news was on statin therapy, other researchers warned that the medical community has problems getting patients to take the treatment.

Researchers at the Cleveland Clinic studied whether “real world” patients achieved the reduced LDL cholesterol levels suggested by package inserts found in the medications. They followed up 375 patients from their institution who were placed on a standard statin dose at entry into a preventive cardiology practice.

Dennis L. Sprecher, MD, section head, Preventive Cardiology and Rehabilitation, at the Cleveland Clinic, said his group found that 66% of patients had less LDL reduction than the package inserts suggested, and 18% experienced no reduction or an increase in LDL.

“We’ve heard that we need to give more drug,” Sprecher said. “Now the question is, ‘If you give it to patients, do they take the drug?’ The answer is a pretty emphatic, ‘No.’”

A current theory to improve patient adherence to a drug regimen centers on empowering patients through education about their medication. But educational efforts are also producing poor results.

Results from the REACH study (Reinforcing Education About Cholesterol and Hypertension for Patients with Coronary Artery Disease) found aggressive educational intervention failed to increase the proportion of patients who reached their target LDL levels.

Investigators at Yale University School of Medicine randomized 756 patients hospitalized at Yale–New Haven Hospital with coronary artery disease to usual care or nurse-based educational intervention. The usual care patients were given materials traditionally received while hospitalized and a

postcard reminder to return for a 1-year follow-up visit. Those in the educational arm received monthly educational mailings and quarterly scheduled phone contacts during which the patients discussed their cholesterol levels and received information about target goals. The study was funded by Pfizer Inc.

At 1 year the two groups were not statistically different—70% of the educated patients reached the LDL target level of less than 100 mg/dL compared with 67% of the usual care patients.

A secondary finding was that the educational effort raised the percentage of patients who knew about the LDL target level from 5% at baseline to 20%. For the usual care patients, the number who knew about LDL target levels increased from 5% at baseline to 7%.

The authors of the study noted the difficulty in lowering patients’ cholesterol levels. Harlan M. Krumholz, MD, of the Yale team, said the medical community needs to continue working on how to improve patient compliance.

“How do you get patients engaged such that they can take some responsibility for the quality of their care?” Krumholz asked. “The medical care system is going to be enhanced on two tracks. One track is for professionals, and the other is for patients. I still believe that. I’m disappointed by these results.”

As for explanations for the REACH results, Krumholz said the education could have been inadequate, or patient knowledge may not translate into reaching targets, or perhaps patient education is ineffective unless it’s integrated into the system of care.

Sprecher said health care professionals may have a hard time discovering a method to improve compliance because of human nature.

“One of the problems that we face is that it’s extraordinarily difficult to get people to do anything on a routine basis,” Sprecher said. “The bottom line is that drugs may be a very complicated way to do chronic therapy.” □